REMARKS

Following entry of the foregoing amendments, claims 44, 47, and 49 to 68 will be pending in the application. Claims 44, 47, 49, and 59 have been amended, herein. No new claims have been added, and no claims have been canceled.

Applicants wish to thank the Examiner for the courteous interview that was held at the Patent Office on October 6, 2005. Applicants appreciate the Examiner's input and helpful comments during the interview. As the Examiner suggestion during the interview, a declaration pursuant to Rule 132 is being submitted herewith to address the enablement rejection. In addition, Applicants have amended the independent claims to add a conclusion step in accordance with discussions that occurred during the interview. The Examiner indicated that the pending claims would likely receive favorable consideration upon submission of the proposed declaration and claim amendments to the Patent Office.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments, the following remarks, and the attached declaration of C. Frank Bennett.

Alleged Lack of Enablement

Claims 44, 47, and 49 to 68 have been rejected under 35 U.S.C. § 112, first paragraph, because the amount of experimentation required for those skilled in the art to practice the claimed methods would allegedly be undue based upon the supposed unpredictability in the art regarding the *in vivo* delivery and efficacy of antisense oligonucleotides. Applicants respectfully traverse the rejection because the specification enables those skilled in the art to practice the full scope of the subject matter recited in the claims without undue experimentation.

Preliminarily, claims 44 and 47 have been amended to recite that the subject compounds comprise a plurality of units linked by covalent linkages in a sequence that are hybridizable to complementary nucleic acids encoding proteins whose production is undesired, and to recite that the compounds interfere with production of the proteins. Claim 49 has been amended to recite that the subject oligonucleotide interferes with production of a protein whose production is undesired, and claim 59 has been amended to recite that

hybridization of the subject oligonucleotide to the sequence-specific ribonucleic acid and concomitant RNase H activation is enhanced. Support of the amendments is found throughout the specification as originally filed. No new matter has been added.

Those skilled in the art following the teachings provided in the specification could readily prepare oligonucleotides that possess the features recited in the claims and exhibit activity *in vivo* against targets of interest. The claims recite methods of treatment and methods for enhancing hybridization and RNase H activation that utilize oligonucleotides that have the following three features: (1) at least one of the nucleotide units of the oligonucleotide is functionalized to increase the nuclease resistance of the oligonucleotide; (2) at least one of the nucleotide units bears a substituent group that increases the binding affinity of the oligonucleotide for its target nucleic acid; and (3) a plurality of the nucleotide units have 2'-deoxy-*erythro*-pentofuranosyl sugar moieties that are consecutively located within the oligonucleotide.

The combination of these three features within a single oligonucleotide imparts unique and beneficial properties to the oligonucleotide. For example, as discussed in the accompanying declaration of C. Frank Bennett, six oligonucleotides possessing these features have been the subject of clinical trials (Bennett Decl., ¶7). Each of the six oligonucleotides is directed against a different molecular target, and has been tested clinically for the treatment of either cancer, rheumatoid arthritis, diabetes, or multiple sclerosis (*id*).

It is thus known in the art that antisense oligonucleotides that possess the three features described above exhibit *in vivo* activity against multiple targets. As confirmed by Dr. Bennett, by following the teachings provided in the specification, those skilled in the art could readily prepare oligonucleotides possessing the three features, and those oligonucleotides would be expected to exhibit antisense activity *in vivo* against targets of interest (*id.*, ¶8). Accordingly, the specification provides sufficient disclosure to teach those skilled in the art how to practice the full scope of the presently claimed methods without undue experimentation.

Although the Office Action asserts that "claims to antisense based pharmaceuticals and method of treating diseases by the administration of said pharmaceuticals are subject to

the question of enablement due to the high level of unpredictability in the antisense art,"[1] as discussed above and in Dr. Bennett's declaration, it has been recognized and reported in the art that antisense oligonucleotides that possess the three features of the oligonucleotides recited in the claims exhibit *in vivo* activity against multiple targets (*id.*, ¶7). The art is thus not unpredictable with respect to the *in vivo* antisense activity of oligonucleotides that possess the three features recited in the claims. The amount of experimentation required to practice the full scope of the claimed methods would therefore not be undue, and Applicants accordingly, respectfully request withdrawal of the rejection.

Alleged Double Patenting

Claims 59 to 68 have been rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 10 of U.S. Patent No. 6,326,199. Without conceding the correctness of the rejection, Applicants submit a terminal disclaimer herewith disclaiming the terminal part of the statutory term of any patent granted on the instant application that would extend beyond the expiration date of the full statutory term, as shortened by any terminal disclaimer, of U.S. Patent No. 6,326,199. The rejection has been obviated, and Applicants respectfully request withdrawal thereof.

[1] Office Action dated May 17, 2005, page 6.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully Submitted,

Date: November 17, 2005

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